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Partial Response Induced by Anti–PD-1-Based Immunotherapy with Toripalimab in a Patient with Locally Advanced Gestational Trophoblastic Neoplasia Who Failed Rapidly of Multiline Chemotherapy: A Case Report

Li Q J and Shi B*

Departments of Integrated Traditional Chinese and Western Medical Oncology, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer hospital, China

***Corresponding author:**

Shi Bian,
Departments of Integrated Traditional Chinese and Western Medical Oncology, The Affiliated Cancer Hospital of Zhengzhou University, Henan Cancer hospital, Zhengzhou, 450008, China,
E-mail: zlyyshibian2800@zzu.edu.cn

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Keywords:

Toropalimab; Choriocarcinoma; PD-1 inhibitor; Gestational trophoblastic tumor

1. Abstract

Immune checkpoint inhibitors (PD-1 inhibitors) are extensively used in cancer treatment. These inhibitors have exhibited definite curative effects in non-small cell lung cancer, Hodgkin's lymphoma, hepatocellular carcinoma, and oesophageal squamous cell carcinoma. However, no comprehensive study has been conducted to evaluate the clinical efficacy of PD-1 inhibitors in the treatment of gestational trophoblastic tumours. A 54-year-old female patient presented with advanced choriocarcinoma and multiple systemic metastases with urinary blood after failed multiline chemotherapy. The clinical survival time was predicted to be approximately 1 month. However, the patient condition was partially relieved after administration of immunotherapy with the PD-1 inhibitor toropalimab. The patient returned to normal life, which confirms the efficacy of the PD-1 inhibitor. In conclusion, although toropalimab has no relevant indications for choriocarcinoma, it can improve patient survival under certain conditions.

2. Introduction

Gestational trophoblastic tumour (GTN) represents the malignant form of Gestational Trophoblastic Disease (GTD). However, 80% of GTD manifestations are benign Hydatidiform Mole (HM), whereas only 20% of patients with GTD develop malignant GTN. GTN is closely related to pregnancy and can be secondary to abortion, full-term pregnancy, ectopic pregnancy, and preterm birth. The main types of GTN are choriocarcinoma, invasive mole, Epithelioid Trophoblastic Tumour (ETT), and Placental Site Trophoblastic Tumour (PSTT). Invasive HM accounts for 15% of all GTDs, whereas choriocarcinoma and other rare GTN subtypes account for the remaining 5% [1]. GTNs are diagnosed by physical examination, medical history examination, and metastatic imaging such as chest, abdominal, or pelvic Computed Tomography (CT) contrast scan [or magnetic resonance imaging (MRI) in the presence of contrast agent contraindication]; brain CT (in the presence of lung metastasis); or brain MRI (the first choice). Biopsy of visible lesions within the lower genital tract is unadvisable because of the risk of bleeding. Additionally, the National Comprehensive Cancer Network (NCCN) guidelines recommend human chorionic gonadotropin (hCG) detection as a vital disease indicator [2]. False hCG elevation may also be considered in case of increase in hCG with no obvious imaging disease evidence [3].

GTN staging has been performed according to tumour extent and location, where stage I refers to lesion in the uterus, stage II refers to direct metastasis or invasion into additional genital structures, stage III involves pulmonary metastasis, and stage IV indicates distant metastasis other than the lung. The FIGO disease prognosis rating system was modified based on the World Health Organisation classification and included prognostic factors in the Bagshawe classification system [4, 5]. The FIGO prognosis scores are determined according to diverse risk factors such as age, prior pregnancy, spacing from first pregnancy, pretreatment hCG, maximum tumour size, metastasis number and location, and prior unsuccessful chemotherapeutic regimes for predicting resistance to mono-chemotherapy for GTN (Table 1) [6]. The sum of individual scores

represented low (< 7), high (≥ 7), and ultra-high (> 12)-risk GTN [7-9]. This prognosis scoring system applies only to choriocarcinoma and invasive HM and not to ITT, ETT, or PSTT [10].

GTN, especially choriocarcinoma with a high degree of malignancy, is gaining attention in medicine. It has an incidence rate of 1/40,000–9.2/40000 and is prone to metastasis [11]; it is characterised by early and extensive metastasis. The most common sites of GTN metastasis include lungs (80%), vagina (30%), pelvis (20%), liver (10%), and brain (10%) [12]. The present study reports a patient with pelvic and lung metastases. Studies have exhibited that vaginal and pelvic metastases have no substantial impact on the prognosis of patients with GTN [13]. Despite a high cure rate (close to 100%) [14], some patients with advanced, high-risk GTN, or even extensive GTN metastasis are not optimally treated. Presently, chemotherapy is the main treatment for patients with high- and low-risk GTN. The main chemotherapy drugs include methotrexate, dactinomycin, and fluorouracil and may be supplemented by surgery, if required [15]. None of the studies have reported the efficacy of immune or targeted drugs in choriocarcinoma.

A few studies have focused on GTN immunotherapy. A study reported four cases of drug-resistant GTN (including two with mixed or metastatic ETT or PSTT and two with metastatic choriocarcinoma) treated by pembrolizumab [16]. The study reported PD-L1 upregulation in these tumours. A sustained pembrolizumab response was observed in three cases. Patients not responding to pembrolizumab exhibited high PD-L1 expression levels but no tumour-infiltrating lymphocytes [16]. Therefore, GTN immunotherapy must be further explored.

Table 1: Scoring system for GTN

Risk factor	Score			
	0	1	2	4
Age, y	≤39	>39	-	-
Antecedent pregnancy	Mole	Abortion	Term	-
Pregnancy event to treatment interval, mo	<4	6-Apr	12-Jul	>12
Pretreatment hCG, mIU/mL	<103	103-104	104-105	>105
Largest tumor mass, including uterus, cm	<3	4-Mar	≥5	-
Site of metastases	-	Spleen, kidney	GI tract	GI tract
No. of metastases	-	4-Jan	8-May	>8
Previous failed chemotherapy	-	-	Single drug	≥2 drugs

Overall scores for patients were acquired through the addition of all prognostic factor scores from different individuals: low risk < 7; high risk ≥ 7; ultra-high risk > 12.

3. Case Report

In June 2017, the pelvic colour Doppler ultrasound of the patient exhibited gestational trophoblastic tumour, whereas the hCG test result was 481759 IU/l. Investigations were conducted, and the patient was diagnosed with choriocarcinoma at the Third Affiliated Hospital of Zhengzhou University. The initial pathology of the patient was unknown, and the data of initial diagnosis were incomplete as the patient was admitted in another hospital previously. Chemotherapy was initiated with 2017.06.20.2017.07.18 FCW (oxaliplatin mannitol + vinoresin + methotrexate) regimen for two cycles after excluding the contraindications to chemotherapy. Then, the patient underwent a successful "abdominal total nephrectomy + bilateral appendectomy + lumen tissue aspiration + intestinal adhesion separation" on 1 August 2017. Postoperative pathology exhibited a partial HM in the uterine cavity, chronic squamous epithelium inflammation of the official neck cyst, and no malignancy in the bilateral eggs and fallopian tubes. Then, the patient underwent five chemotherapy cycles with actinomycin D + vincristine + fluorouracil on 18 August 2017, 7 September 2017, 26 September 2017, 18 October 2017, and 17 November 2017. The patient then underwent pelvic radiotherapy of DT50Gy because the decrease in hCG was not ideal. Afterwards, the patient underwent eight more chemotherapy cycles with ifosfamide + etoposide on 12 March 2018, 2 April 2018, 23 April 2018, 21 May 2018, 16 June 2018, 2 July 2018, 28 September 2018, and 18 October 2018. On 19 November 2018, the patient underwent a second surgical procedure, namely laparoscopic vaginal stump resection + paravaginal extensive resection + intestinal adhesion lysis + pelvic adhesion lysis under general anaesthesia. The first postoperative pathological examination (12 November 2018-98439) of the vaginal stump exhibited a gestational trophoblastic tumour. Immunohistochemistry was recommended to assist in classification. The left ureteral mass exhibited fibrous adipose tissue with haemorrhage, focal with linear junction reaction, and no tumour involvement. The second pathological examination of the vaginal stump exhibited gestational trophoblast tumour, no placental villi consistent with choriocarcinoma, and vascular tumour thrombus. Immunohistochemistry exhibited AE1/AE3 (+), EMA (-), hCG (+), PLAP (-), HPL (-), and Ki-67 (80%+). Postoperative recovery was acceptable. Then, two cycles of "ema-ep" chemotherapy were administered on 6 December 2018 and 25 December 2018. Intravenous bone marrow suppression occurred after chemotherapy. At this time, the patient felt tired and wished to change to a professional hospital to continue treatment. After 2 months of rest, the patient visited our hos-

pital on 4 March 2019. External CT examination was performed, which exhibited pulmonary metastasis and left pyeloureteral dilatation. Two EMA-CO chemotherapy cycles were administered on 6 March 2019 and 27 March 2019. The patient exhibited bleeding from the bladder on admission and underwent enhanced CT test (Figure 1A and Figure 1B).

Efficacy and disease progression were evaluated on CT. Then, three cycles of Anlotinib combined with paclitaxel + cisplatin + etoposide chemotherapy were administered, followed by postanlotinib monotherapy maintenance therapy. The patient condition improved slowly (Figure 2).

In October 2020, the patient experienced headache, and MRI of the head exhibited brain metastasis (Figure 3).

On 22 October, 2019, head radiotherapy was performed for one cycle, after which the patient was hospitalised for multiple times due to urinary blood and received symptomatic support treatment with blood transfusion. Anlotinib was stopped intermittently, and the condition continued to improve slowly (Figure 4).

In January 2020, the patient was hospitalised again and recommended active treatment. PD-L1 expression, gene, and tumour mutation load were not observed in the past. Thus, immunotherapy combined with anlotinib targeted therapy was initiated this time. On 4 January 2020, toropalimab combined with anlotinib immunotargeted therapy was initiated, with a cycle of 28 days. After 2 cycles, the patient did not urinate blood again, and the anaemia improved significantly. Re-examination exhibited that the haemoglobin level was normal. The survival time was approximately 3 months. However, after treatment, the patient recovered and resumed normal life. The PS score decreased from 2 to 1 (Figure 5).

The lung metastases after immunotherapy in March, June, and September 2020 were smaller than those in December 2019. No obvious bladder invasion and urinary blood were observed during the period. Partial Remission (PR) was observed. Then, the patient continued to use toropalimab until January 2021. Immunotherapy combined with anlotinib anti-angiogenesis therapy was administered for a year, and the review exhibited Stable Disease (SD). Then, toropalimab was changed to be used during review, and only toropalimab was used for maintenance treatment (figure 6).

The patient was treated with toropalimab for more than 1.5 years and has achieved PR. Thus, immunotherapy improved the patient prognosis. Further follow-up studies and more clinical studies on the application of immunotherapy in choriocarcinoma are required.

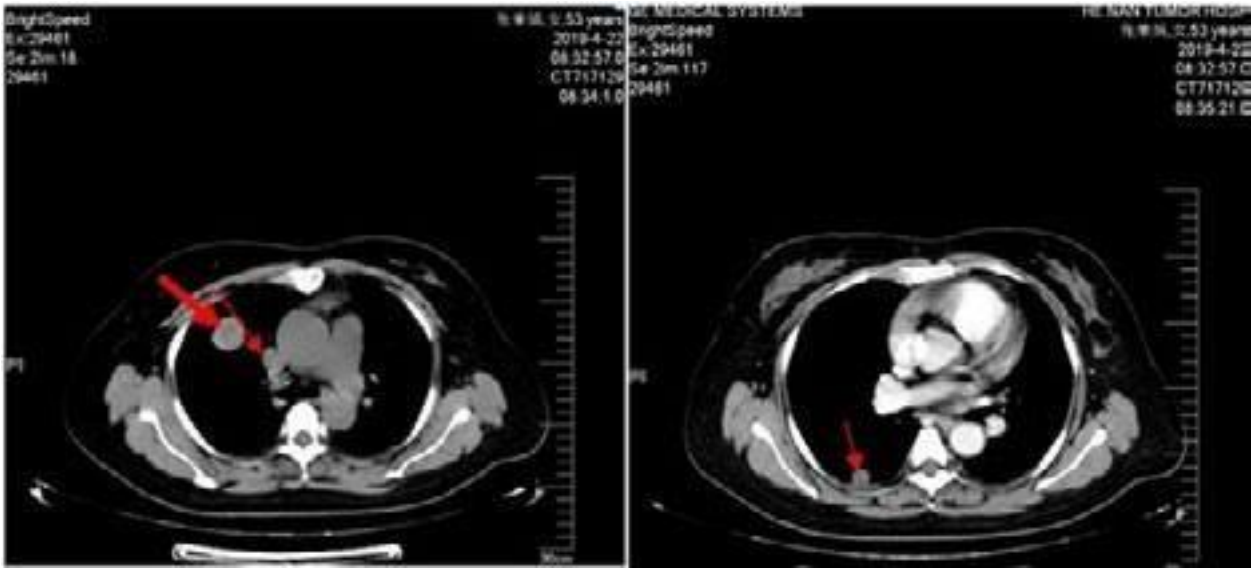


Figure 1: A/B.Chest enhanced CT scan

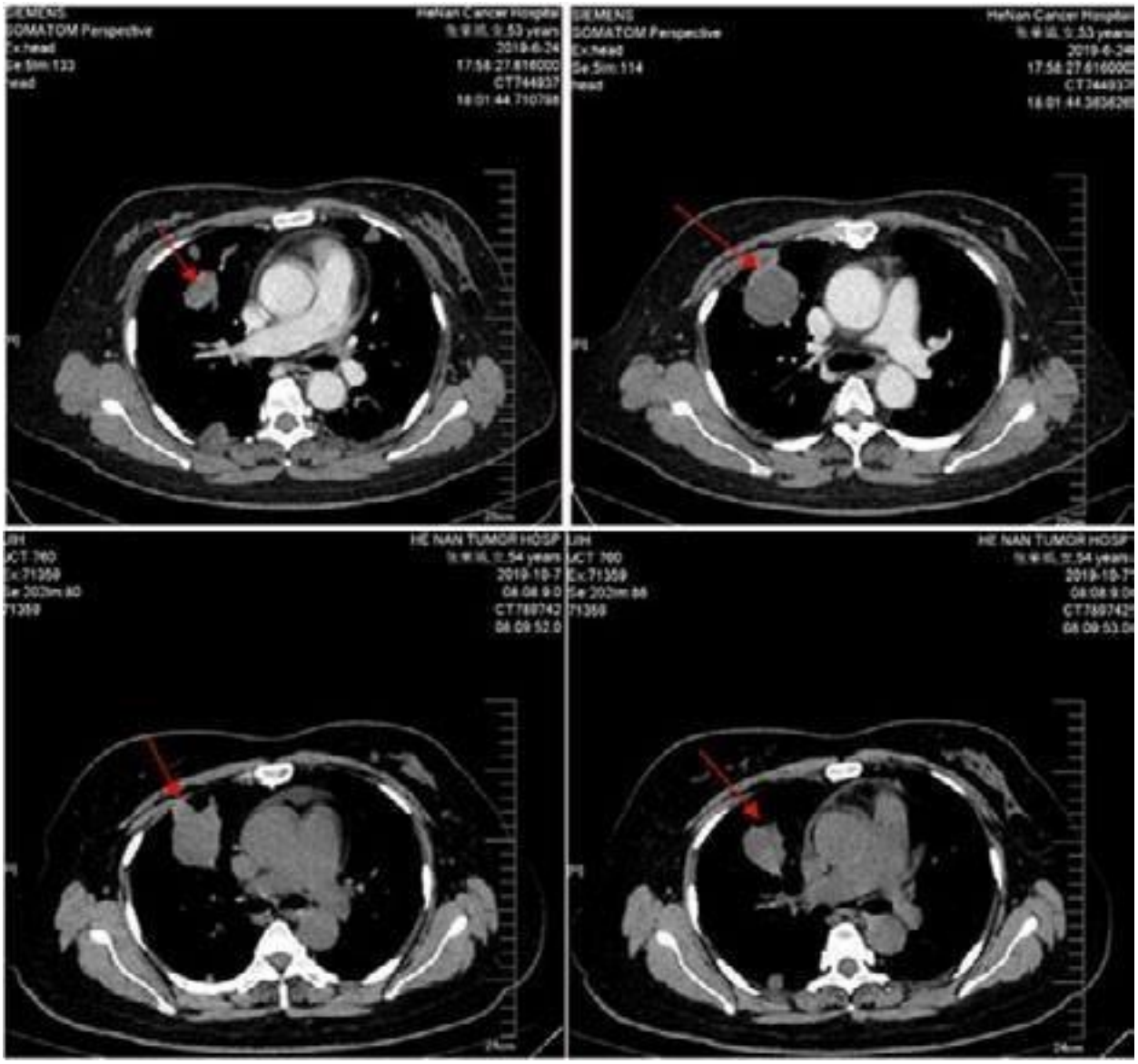


Figure 2A/2B/2C/2D: Pelvic enhanced CT scan after Anlotinib monotherapy maintenance therapy

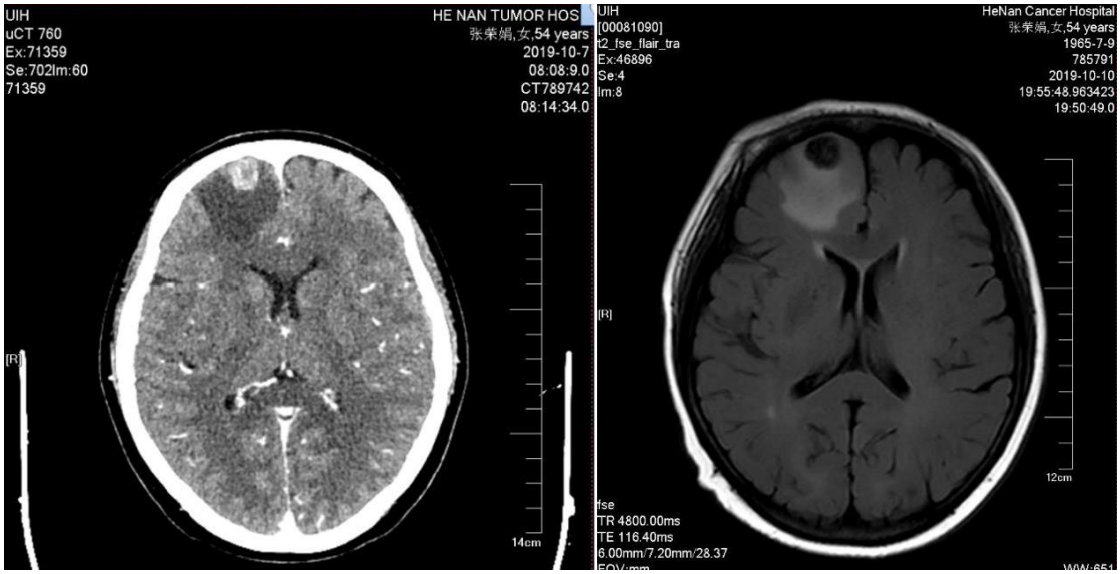


Figure 3A/3B/3C: Brain CT scan

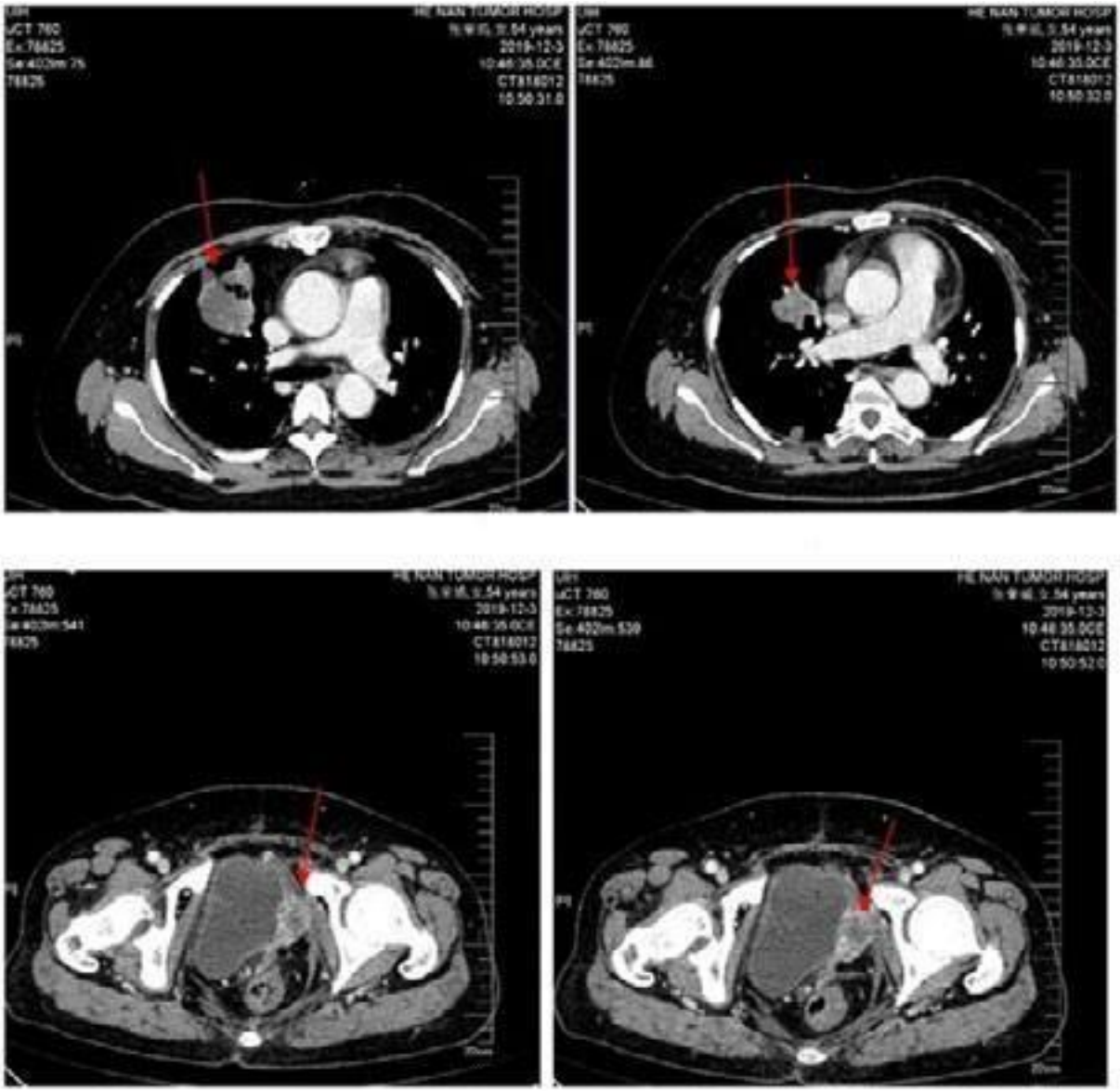
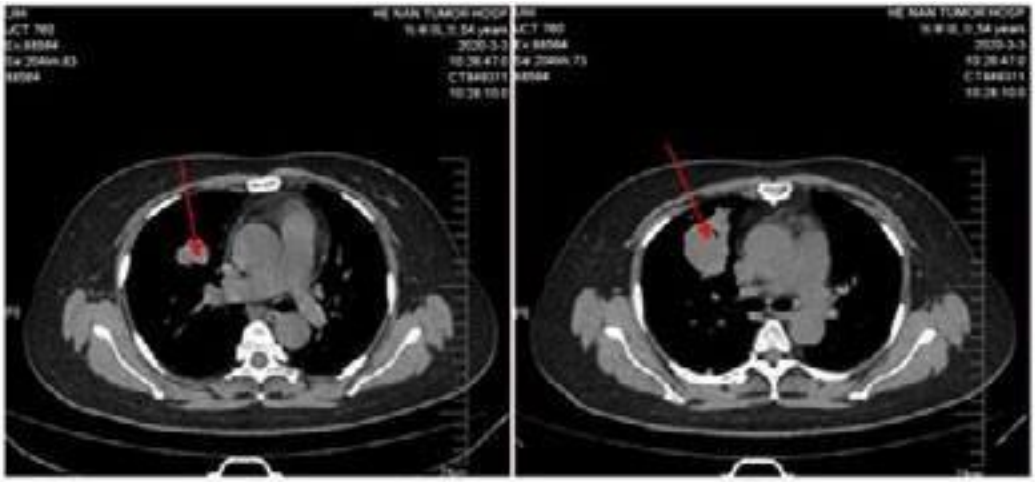
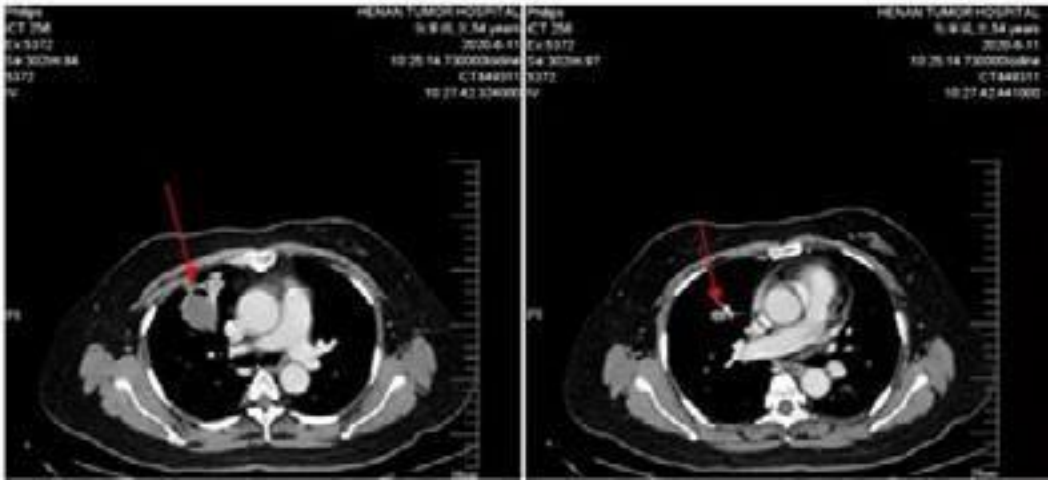
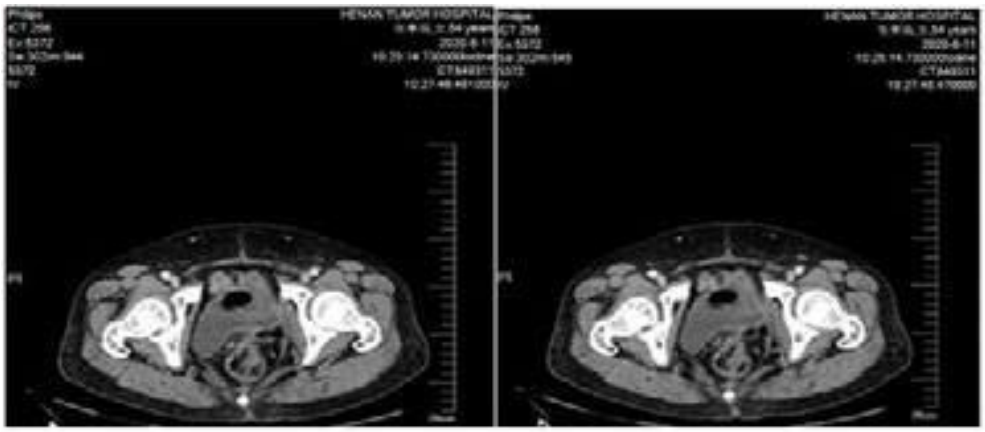
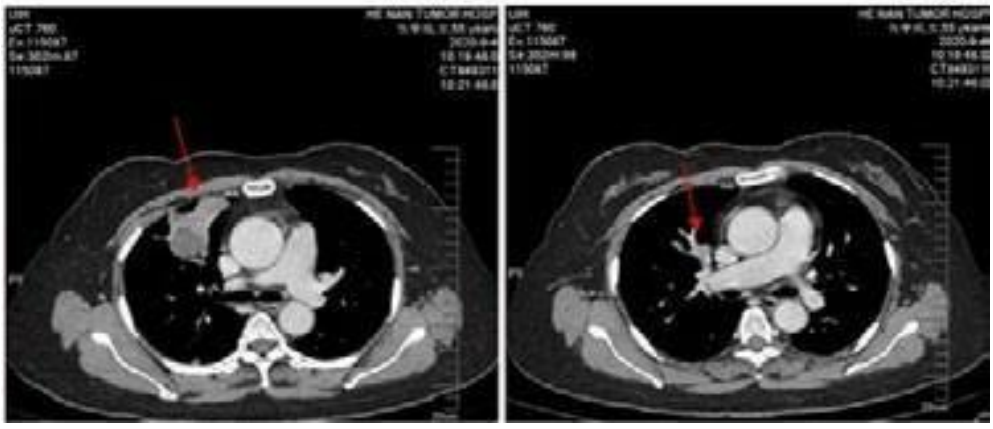


Figure 4A/4B/4C/4D: CT scan after head radiotherapy and anlotinib









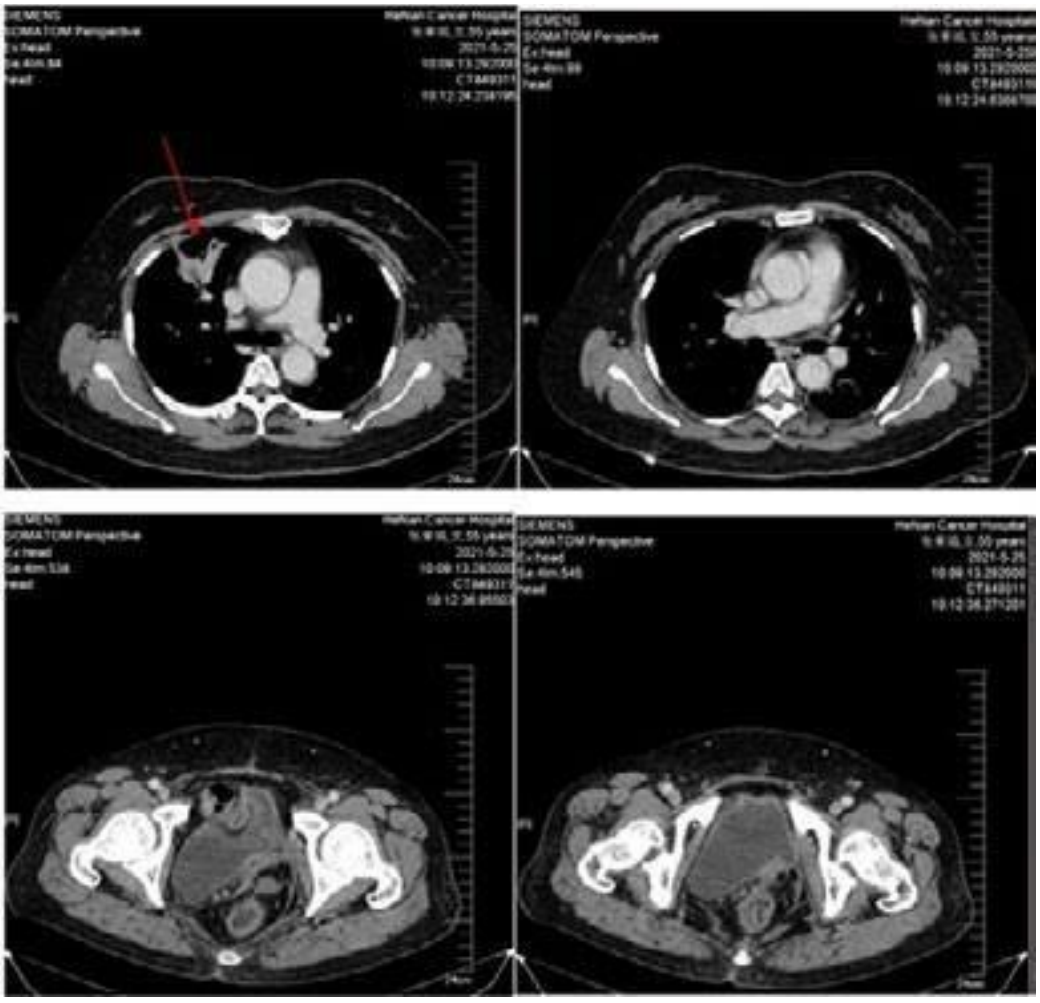


Figure 5A/5B/5C/5D/5E/5F/5G/5H: CT scan after toropalimab

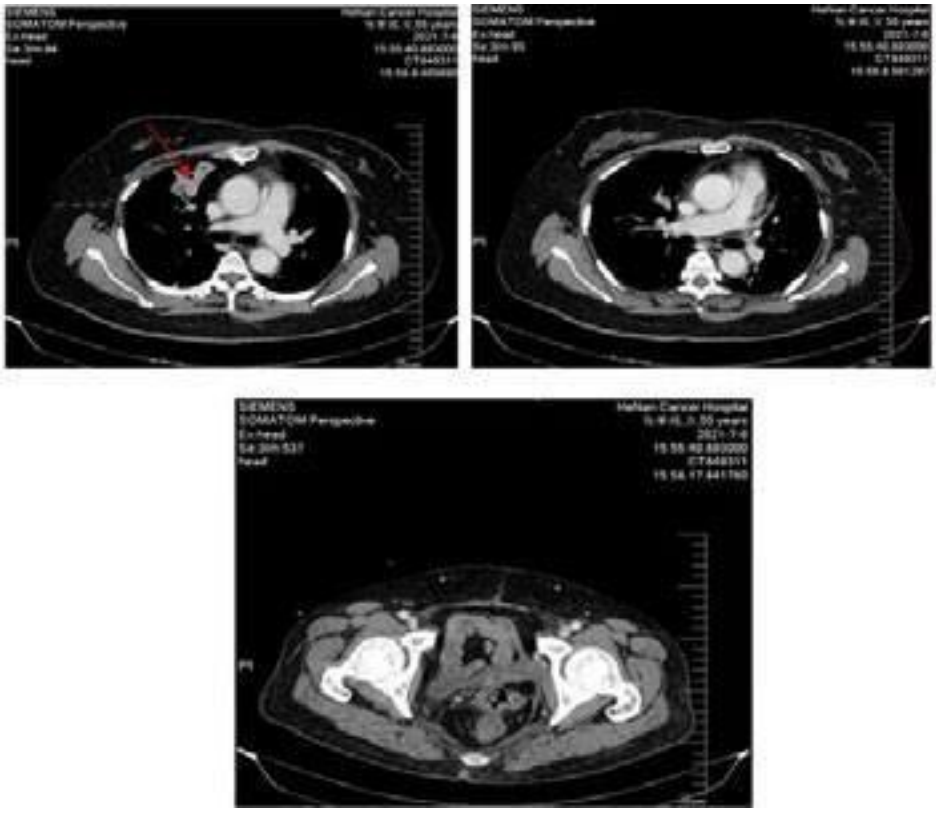


Figure 6:

4. Discussion

The 54-years-old patient in the present study had typical high-risk GTN and was diagnosed with choriocarcinoma in June 2017. The patient exhibited multiple systemic metastases after being transferred to our hospital, with a FIGO score of 13. Although the initial treatment regimen was incomplete, it generally followed the sequential treatment regimen according to NCCN guidelines. The initial treatment was chemotherapy using CMV regimen (oxaliplatin mannitol + vincristine + methotrexate) for two cycles, supplemented by surgery. Subsequently, chemotherapies such as "dactinomycin+ vincristine + fluorouracil", "ifosfamide + etoposide", EMA/EP, and EMA/CO were adopted, although these therapies exhibited unsatisfactory results. CT indicated that the disease was progressing slowly, and the hCG decline was not ideal. When the standard treatment regimen was ineffective, the patient actively cooperated with the treatment, and the targeted drug anlotinib was used for experimental treatment. However, the effect was unsatisfactory, and the patient was not sensitive to anlotinib. The patient was continued to be actively treated, and the immunotherapy regimen with toropalimab (3 mg/kg, IV, once at intervals of 4 weeks) was initiated on 4 January 2020.

Toropalimab, the selectively recombinant humanised anti-PD-1 monoclonal antibody, can combine with PD-1 onto the activated T cells to block PD-1 interactions with PD-L1 and PD-L2. Toropalimab was developed by Shanghai Junshi Biotechnology Co. Ltd. (Junshi Bio) [17, 18]. Toropalimab was originally approved in China on December 2018 for treating metastatic or unresectable melanoma unresponsive to previous systemic treatments [18]. Toropalimab has not been approved for use in other cancer types, and relevant clinical studies and experimental data are required in the future. A phase I study on refractory malignancies exhibited that toropalimab demonstrated a good safety profile, with adverse events of grade 1–2. Fatigue was the most common immune-related adverse reaction, which was the main reason for selecting toropalimab for immunotherapy in the present study. Additionally, toropalimab demonstrated high efficacy in 127 patients with advanced melanoma who had failed systemic therapy. Among these, 1, 21, and 51 patients achieved complete remission (CR), PR, and SD, respectively, with an objective remission rate of 17.3%. Additionally, the disease control rate was 57.5% [19]. Thus, toropalimab is effective in treating malignant tumours. However, the efficacy of toropalimab on choriocarcinoma has not been studied, and no typical reference plan is available for this case. After failure of the standard sequential treatment plan, toropalimab was successfully applied as a PD-1 immunoinhibitor for immunotherapy. The patient has achieved PR.

Early chemotherapy is generally administered by following the guidelines; however, the dosage and cycle may not be well controlled when using chemotherapy drugs alternately, resulting in the patient condition not being effectively controlled. Despite multidrug treatment, approximately 30%–40% of high-risk cases reported incomplete remission after first-line treatment or disease recurrence [20, 21]. Several cases developed multiple metastatic lesions at the non-pulmonary and non-vaginal sites, most of who were initially treated inadequately [22, 23]. This may have been the case in the patient reported in this case as the disease progressed to an extensive stage and developed resistance to several classic chemotherapy drugs. The EP/EMA or EMA/EP regimen has been recognised as the preferred option for cases responsive to EMA/CO or those with re-elevated hCG after they achieve CR following EMA/CO [24, 25]. EMA/EP provides a CR rate between 75% and 85% in EMA/CO-resistant diseases [24-28]. Other drug combinations that include platinum and etoposide agents such as BEP (bleomycin, etoposide, and cisplatin), TP/TE (paclitaxel/cisplatin and paclitaxel/etoposide that alternate on the weekly basis), ICE (ifosfamide, carboplatin, and etoposide), and VIP (etoposide, ifosfamide, and cisplatin) are effective in cases developing resistance to methotrexate-based regimens [28-31]. Additionally, TIP (paclitaxel, ifoshamide, cisplatin) is adopted to be the remedial chemotherapy regimen for germicellular tumours such as choriocarcinoma [32-34]. These protocols containing etoposide-platinum need to be supported with granulocyte colony-stimulating factor to prevent treatment failure due to neutropenia complications [29, 30, 35]. The overall success rate of treatment in these patients is approximately 80%. However, factors such as pretreatment, elevated hCG, multiple metastatic sites, metastasis to non-pulmonary or non-vaginal sites (stage IV), or FIGO score >12 exhibit greater risk of treatment failure. The patient in the present study was treated with immunotherapy when conventional therapies had failed.

Toropalimab could control the disease because the patient was exposed to tumour antigens during chemotherapy, and T cells could effectively kill tumour cells under the action of PD-1 inhibitors. However, the specific mechanism of action remains to be further explored. Toropalimab exhibited superior efficacy in choriocarcinoma treatment. The patient is returning to normal life and is stable, has achieved PR, and is expected to achieve CR. Further follow-up of the patient is required to obtain data and evidence for the treatment of patients with ultra-high risk choriocarcinoma.

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